REMARKS

Claims 33-64 are pending. Claims 33-64 were rejected under 35 U.S.C. §112, first paragraph. Claims 33-53 were rejected under 35 U.S.C. §112, second paragraph. Claims 33-49, 51-61 and 64 were variously rejected under 35 U.S.C. §103(a).

Claims 33-40, 47, 51-53, 58 and 59 have been canceled, claims 41-46, 48-50, 54-57 and 60-64 have been amended and new claims 65-73 have been added herein without prejudice or disclaimer of any previously claimed subject matter.

Support for the amendments and new claims can be found throughout the specification. For example, support for amendment to claims 54, 60, 61 and 64 is found, *inter alia*, at page 4, lines 28-31 and page 15, lines 21-30. Support for the amendment to claim 55 is found, *inter alia*, at page 4, lines 16-20 and in originally filed claim 16. Support for the amendment to claims 56 and 57 and new claims 72 and 73 is found, *inter alia*, at page 4, lines 31-35 and originally filed claim 22. Support for new claim 65 is found, *inter alia*, at page 4, lines 28-31; page 6, lines 19-30; page 6, line 35 through page 7, line 31 and page 15, lines 21-30. Support for new claims 66 and 67 is found, *inter alia*, at page 7, lines 26-31 and in originally filed claim 12. Support for new claims 68-71 is found, *inter alia*, at page 7, lines 2-5.

The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and canceled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover has not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is entitled "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**".

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Rejections under 35 U.S.C. §112, first paragraph

Claims 33-64 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled commensurate in scope with the claims. Applicants respectfully traverse this rejection.

With respect to the examined claims 33-64, Applicants submit that the claims were in compliance with the enablement requirement for the reasons of record outlined in the Amendment and Response submitted July 24, 2001.

In the interest of promoting prosecution of this application, claims 33-64 have been amended or canceled without prejudice or disclaimer of any previously claimed subject matter. With regard to the amendments and canceled claims, Applicants reserve the right to pursue prosecution of any presently excluded subject matter in one or more future continuation and/or divisional applications.

The present invention is directed to a method for facilitating survival of an allogeneic graft through administering retinal pigment epithelial (RPE) cells and a population of non-RPE cells to a site in a mammal, wherein the non-RPE cells are allogeneic to the mammal, thereby increasing survival time of the population of non-RPE cells. The invention is also directed to pharmaceutical compositions and kits including RPE cells and allogeneic non-RPE cells for use in the method.

Applicants respectfully submit that the pending claims are in compliance with the enablement requirement.

Applicants respectfully request that the rejection of claims under 35 U.S.C. §112, first paragraph, be withdrawn.

Rejections under 35 U.S.C. §112, second paragraph

Claims 33-53 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this ground for rejection.

With regard to claim 33, the Examiner finds that the metes and bound of "co-administering" and "immune-privileged site" cannot be determined.

Applicants submit that claims 33-53 are not indefinite for use of the term "co-administering." The specification states that the RPE cells and the non-RPE cells "may be co-administered either as a single composition, or alternatively, as separate compositions" (page 4, lines 22-23). The specification also states that the RPE cells "may be administered prior to co-administration" of the non-RPE cells (page 4, line 25). Thus, the term "co-administering" refers to administration of RPE cells and non-RPE cells to a site in the mammal such that the RPE cells facilitate survival of the non-RPE cells, even if the two cell populations are administered at different times.

Thus, Applicants submit that the term "co-administering" is sufficiently definite when considered in view of the specification and the understanding of those skilled in the art. Nevertheless, in order to enhance clarity, the claims have been amended to a method which comprises administering RPE cells and a population of non-RPE cells to a site in a mammal.

Applicants also submit that the phrase "immune-privileged site" is sufficiently definite when considered in view of the specification and the understanding of those of skill in the art. Nevertheless, Applicants have attempted to respond to each of the various concerns of the Examiner in the pending claims in order to facilitate disposition of the present case.

In view of the foregoing amendments and remarks, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 33-53 under 35 U.S.C. §112, second paragraph.

Rejections under 35 U.S.C. §103

Claims 33-38, 41-49, 51-61 and 64 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Cherksey (U.S. Patent 5,618,531). Claims 33, 39 and 40 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Cherksey in view of Goldstein et al. (U.S. Patent 5,300,436, "Goldstein"). Applicants respectfully traverse these grounds for rejection.

Applicants have cancelled claims 33-40, 47, 51-53, 58 and 59 without prejudice or disclaimer, rendering this ground for rejection moot as it pertains to those claims. With regard to the remaining claims, Applicants respectfully point out that the cited references do not support a *prima facie* case of obviousness with regard to the claimed invention.

The present invention is based on the discovery that retinal pigment epithelial (RPE) cells secrete an immunosuppressive cytokine, Fas L, and can thereby produce a localized immunosuppressive environment at the site of RPE cell implantation. The invention is directed to a method for facilitating survival of an allogeneic graft through administering RPE cells and a population of non-RPE cells to a site in a mammal, wherein the non-RPE cells are allogeneic to the mammal, thereby increasing survival time of the population of non-RPE cells. Thus, when RPE cells and allogeneic, non-RPE cells are co-administered to a site, the RPE cells provide localized immunosuppression that facilitates survival of the non-RPE cell graft. The invention is also directed to pharmaceutical compositions and kits including RPE cells and allogeneic non-RPE cells for use in the method.

Cherksey teaches administration of matrix-attached neural or paraneural cells, including RPE cells, to the brain for the treatment of a neurological disease. Cherksey also describes "co-culture of neural or paraneural cells with glial cells, their co-incubation with a support matrix, followed by implantation of the support matrix carrying both cell types" (column 9, lines 3-6). As noted in Cherksey (column 8, line 65 through column 9, line 2), transplantation of glial cells

into the brain was known in the art. Thus, Cherksey describes implantation of a support matrix carrying cell types which are known to survive implantation into the brain.

However, Cherksey does not teach or suggest that cells can secrete Fas L to create localized immunosuppression, much less that RPE cells secrete Fas L. Cherksey provides no guidance for the selection of RPE cells for the purpose of the present invention. Thus, there is no motivation, either in the art or in the reference itself, for one skilled in the art to modify Cherksey to arrive at the presently claimed invention, i.e., administering RPE cells and allogeneic non-RPE cells to a site in a mammal to facilitate survival of the allogeneic graft.

Accordingly, Cherksey does not support *prima facie* obviousness with regard to the claimed invention.

Goldstein teaches transfecting a tyrosine hydroxylase gene into cells, including RPE cells, and transplanting the genetically altered cells into the brain. Goldstein does not address the fundamental deficiencies of Cherksey in the Office's contention of obviousness. Goldstein does not teach co-administration of RPE cells and non-RPE cells wherein the non-RPE cells are allogeneic to the mammalian recipient of the cells. Goldstein contains no disclosure with regard to use of RPE cells for facilitating survival of an allogeneic graft. Thus, Goldstein in combination with Cherksey does not teach or suggest the claimed invention.

Accordingly, Applicants respectfully point out that the cited references do not support *prima facie* obviousness with regard to the claimed invention.

Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §103.

CONCLUSION

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is

respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' agent at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 311772000500. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please enter the following amendments without prejudice or disclaimer.

In the Claims:

Please amend claims 41-46, 48-50, 54-57 and 60-64 as follows.

41. (Twice Amended) The method of claim [33] 65 wherein said RPE cells or [said] cells of said population of non-RPE cells [cell population] are attached to a matrix prior to administration.

42. (Twice Amended) The method of claim [33] 65 wherein said RPE cells and [said] cells of said population of non-RPE cells [cell population] are attached to a matrix prior to administration.

43. (Amended) The method of claim [33] 65 wherein said administering [and said co-administering] is by transplantation.

44. (Amended) The method of claim [33] 65 wherein said RPE cells are administered in a dose ranging from 10^3 to 10^7 cells.

45. (Twice Amended) The method of claim [33] 65 wherein said non-RPE cell population is [co-administered] administered in a dose ranging from 10^3 to 10^7 cells.

46. (Amended) The method of claim [33] 65, further comprising re-administering RPE cells to the site in an effective amount to sustain [the immune-privileged site] survival of the allogeneic non-RPE cells.

48. (Twice Amended) The method of claim [33] 46 [further comprising re-administering RPE cells and cells of said non-RPE cell population in amounts effective to sustain a therapeutic effect,] wherein the RPE cells for re-administration [and the cells of the non-RPE cell population] are attached to a matrix prior to re-administration.

49. (Twice Amended) The method according to claim [33] 65 wherein the RPE cells and the population of non-RPE cells [cell population] are [co-administered] administered as a single composition.

50. (Twice Amended) The method according to claim [33] 65 wherein the RPE cells and the population of non-RPE cells [cell population] are [co-administered] administered as separate compositions.

54. (Twice Amended) A pharmaceutical composition comprising retinal pigment epithelial (RPE) cells, a non-RPE cell population, and a pharmaceutically acceptable carrier,

wherein said non-RPE cell population is allogeneic to said RPE cells and wherein the ratio of RPE cells to non-RPE cells is sufficient to be useful in the method of claim 65 [said non-RPE cell population produces a biologically active molecule that is absent or defective in a disease].

55. (Amended) The composition of claim 54 wherein said population of non-RPE cells produces a biologically active molecule that is absent or defective in a disease [biologically active molecule is a neurotransmitter].

56. (Amended) The composition of claim 54 wherein said [biologically active molecule is a hormone] non-RPE cell population comprises insulin-producing cells.

57. (Amended) The composition of claim [54] 56 wherein said insulin-producing cells are pancreatic islet of Langerhans cells [biologically active molecule is a cytokine inhibitor].

60. (Twice Amended) A pharmaceutical composition comprising retinal pigment epithelial (RPE) cells and a non-RPE cell population, wherein said non-RPE cell population is allogeneic to said RPE cells, wherein the ratio of RPE cells to non-RPE cells is sufficient to be useful in the method of claim 65 [said non-RPE cell population produces a biologically active molecule that is absent or defective in a disease] and wherein said RPE cells and [the] cells of the population of non-RPE cells [cell population] are attached to a matrix.

61. (Twice Amended) A compartmentalized kit adapted to receive a first container adapted to contain retinal pigment epithelial (RPE) cells and a second container adapted to contain a non-RPE cell population, wherein said RPE cells are allogeneic to said non-RPE cell population and wherein the ratio of RPE cells to non-RPE cells provided in the kit is sufficient to be useful in the method of claim 65 [said non-RPE cell population produces a biologically active molecule that is absent or defective in a disease].

62. (Twice Amended) [A] The compartmentalized kit according to claim [60] 61, wherein the non-RPE cell population comprises insulin-producing cells.

63. (Amended) [A] The compartmentalized kit according to claim 62, wherein the insulin-producing cells are pancreatic islet of Langerhans cells.

64. (Twice Amended) An article of manufacture, comprising:

a packaging material;

retinal pigment epithelial (RPE) cells contained within said packaging material[, wherein said RPE cells are effective for creating an immune-privileged site in a mammal];

a non-RPE cell population contained within said packaging material, [wherein said non-RPE cell population produces a biologically active molecule and] wherein said non-RPE cell population is allogeneic to said RPE cells;

wherein the ratio of RPE cells to non-RPE cells contained within said packaging material is sufficient to be useful in the method of claim 65; and

wherein said packaging material contains a label that indicates that said RPE cells can be used for [creating an immune-privileged site] facilitating survival of an allogeneic graft in a mammal.